Settlement Agreement in Litigation Against EPA's Human Studies Rule

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Overview

- Litigation History
- Terms and Impacts of the Settlement Agreement
- Rulemaking Schedule

EPA's 2006 Rule: "Protections for Subjects in Human Research"

- Promulgated in February 2006
- Modeled on the Common Rule
- Prohibits reliance on research involving intentional exposure of children and pregnant and nursing women
- Requires review of protocols for proposed research by EPA & the HSRB
- . . . and more!

Legal Challenge

- Lawsuit filed against EPA in Spring 2006 by
  - Natural Resources Defense Council, Inc.
  - Pesticide Action Network of North America
  - Pineros y Campesinos Unidos del Noroeste
  - Physicians for Social Responsibility
  - Farm Labor Organizing Committee of the AFL-CIO
  - Migrant Clinicians Network
- Sen. Barbara Boxer, Sen. Bill Nelson, Rep. Henry Waxman, and Rep. Hilda Solis filed as *amici curiae* in support of petitioners

Petitioners' Core Arguments

- The scope of the rule was inconsistent with the requirements of the 2006 Appropriations Act
- The substance of the rule was inconsistent with
  - The principles proposed in the 2004 NAS report
  - The principles of the Nuremberg Code

Litigation Chronology

- Briefs and oral argument before U. S. Court of Appeals for the Second Circuit – Fall 2006 through January 2008
- Litigation stayed to permit settlement negotiations in April 2009
- Settlement negotiations April 2009 through June 2010
- Settlement agreement filed June 18, 2010; available at: http://www.epa.gov/oppfead1/guidance/human-studies-settlement.pdf
- Litigation further stayed in June 2010 to allow implementation of the settlement agreement

Settlement Agreement

- Defines schedule for proposed and final amendments to the 2006 rule
- Attachment contains negotiated rule language to be proposed for public comment
- If EPA does not comply, petitioners' recourse is to reopen lawsuit
- Negotiated amendments address petitioners' core legal challenges:
  - Scope to cover all EPA regulatory statutes
  - Consistency with NAS recommendations
  - Consistency with Nuremberg Code

Scope of the 2006 Rule

- 2006 Rule applies to research—
  - Involving intentional exposure of a human subject and
  - Intended for consideration under the pesticide laws (subparts K, L, M) or
  - relied on by EPA under the pesticide laws (subparts P & Q)
- Petitioners' concern: the 2006 rule text left a loophole for unethical human pesticide research to be conducted and submitted to EPA and relied on by EPA under other regulatory statutes, and thus to escape regulation

Proposed Scope Changes

- Subpart K "applies to all research initiated after [effective date of amended rule] involving intentional exposure of a human subject to a pesticide if . . . any person who conducted or supported such research intended . . . to submit results of the research to EPA for consideration in connection with any action that may be performed by EPA under any regulatory statute administered by EPA . . ."
- Subparts L, M, and Q have similar changes

Proposed Scope Changes (2)

- For research submitted/considered under FIFRA or FFDCA:
  - Amended rule would apply to all 3rd-party research involving intentional exposure of a human subject
  - Scope would not change from 2006 rule
- For research submitted/considered under any other EPA regulatory statutes:
  - Rule would apply to 3rd-party research involving intentional exposure of a human subject to a pesticide
  - "Pesticide" defined as in FIFRA—a substance or mixture intended for pesticidal effect
  - Rule would not apply to research with multi-use chemicals (like formaldehyde or sulfur) unless they are tested as a pesticide

Impact of Scope Changes

- EPA expects very little impact
- EPA has seen no study "involving intentional exposure of a human subject to a pesticide" that was not covered by the 2006 rule

Consistency with NAS Principles

- The 2006 rule follows the NAS recommendation to start from the Common Rule to protect subjects of 3rd-party research involving intentional exposure
- The 2006 rule does not include rule text specific to most of the 17 NAS recommendations
- Petitioners' concern: the 2006 rule does not require EPA to follow the NAS recommendations

Proposed Changes: Science

- EPA will propose to list in subpart P scientific issues that the Agency must address when reviewing proposed research:
  - Need for human research involving intentional exposure
  - Appropriateness of research design
  - Representativeness of study participants
  - Statistical adequacy of study design
  - Good clinical practice guidelines and safety monitoring, if applicable

Proposed Changes: Ethics

EPA must consider in protocol review:

- Adequacy of previous animal studies
- Adequate identification and minimization of subject risks
- Appropriate balance of risks & benefits
- Equitable subject selection
- Free & fully informed consent
- IRB review and approval
- Adequate protection for potentially vulnerable subjects
- Adequate protection for potentially sensitive subjects
- Appropriate and non-coercive payments to subjects
- Provision of medical care for research-related injuries

Consistency with Nuremberg Code

- Like the Common Rule, EPA's 2006 rule allows a "legally authorized representative" to consent on behalf of a test subject who lacks capacity to provide informed consent
- Petitioners argue this provision is inconsistent with the Nuremberg Code (1947) which states:

> "The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent . . . ."

Changes Re: Surrogate Consent

- EPA will propose to delete from the 2006 rule all references to the provision of informed consent by a "legally authorized representative"
- EPA expects this change to have negligible impact

New Provisions Affecting HSRB

- **§ 26.1606 Human Studies Review Board review of proposed human research.** In commenting on proposals for new research submitted to it by EPA, the Human Studies Review Board shall consider the scientific merits and ethical aspects of the proposed research, including all elements listed in section 26.1603(b) and (c) and any additional conditions recommended pursuant to sec. 26.1603(d).

- **§ 26.1607 Human Studies Review Board review of completed human research.** In commenting on reports of completed research submitted to it by EPA, the Human Studies Review Board shall consider the scientific merits and ethical aspects of the completed research, and shall apply the appropriate standards in Subpart Q.

New Acceptance Standards

- EPA will propose to revise the substantive standards for relying on covered, completed research:
  - Adding a categorical prohibition against reliance on "scientifically invalid research" or data that are not "relevant to a scientific or policy question important for EPA decision-making"

Revised Acceptance Standards

- EPA will propose to change §26.1704:

  EPA shall not rely on research "if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (e.g., the research was intended to seriously harm participants or failed to obtain informed consent), or was deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm (based on knowledge available at the time the study was conducted) or impaired their informed consent."

- EPA will propose parallel changes to §26.1705

Impact of Changes to Subparts P & Q

- EPA expects no impacts on third parties or on the HSRB
- EPA expects to add further detail to its scientific and ethical reviews of proposed and completed research to address specifically the elements that would be required by the proposed amendments

Final Points

- These changes would only apply prospectively
- EPA plans to propose a few additional changes to correct minor errors in the 2006 rule, and may propose other changes that would not affect third parties, EPA or the HSRB substantively, such as adding references to guidance documents or revising the organization of the rule

Rulemaking Schedule

- Proposed rule – signed by January 18, 2011, and published for public comment
- Final rule – signed by December 18, 2011
- The 2006 rule will remain in effect until it is replaced by a new final rule